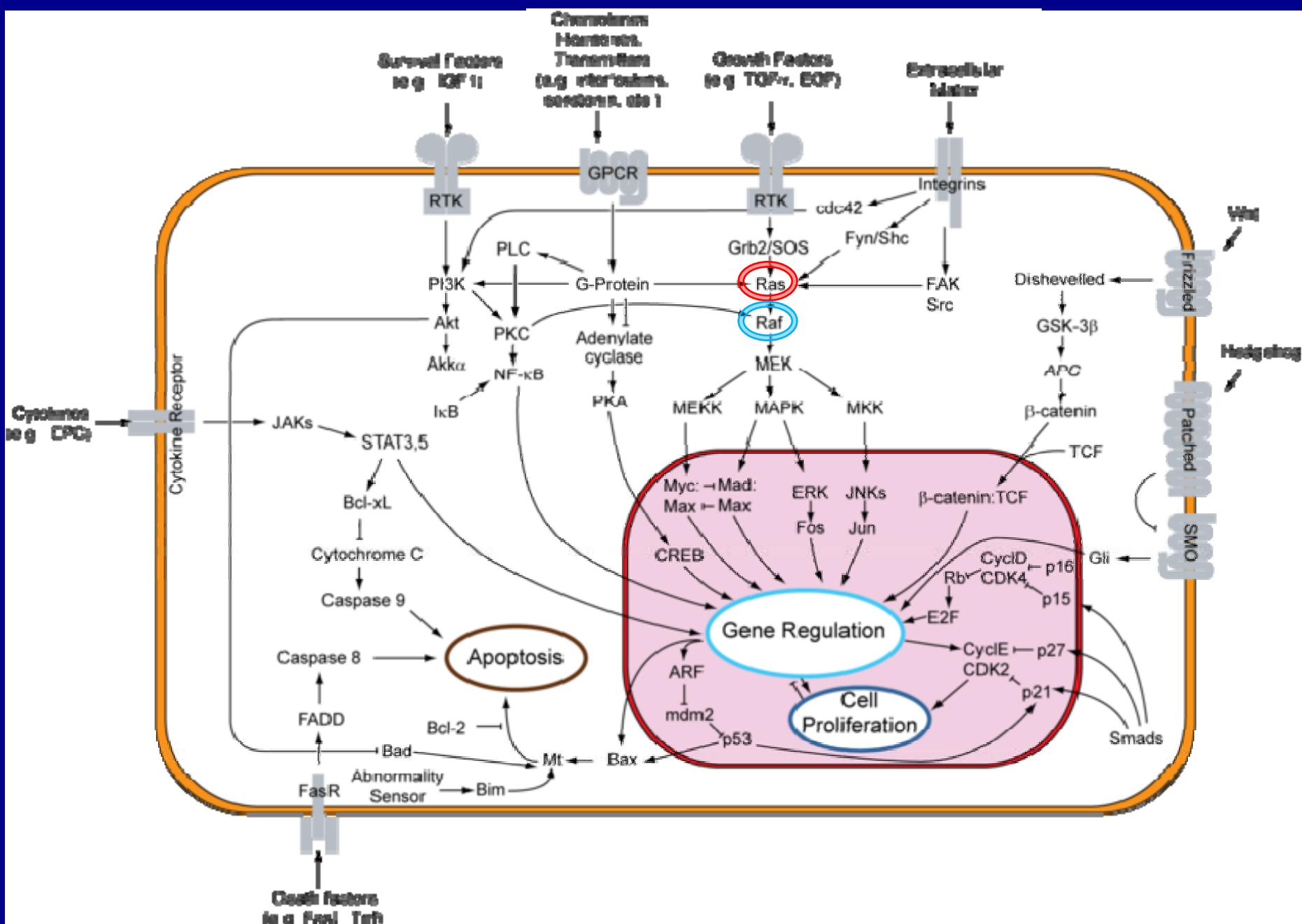


Development of Trametinib in Pediatric Tumor Indications

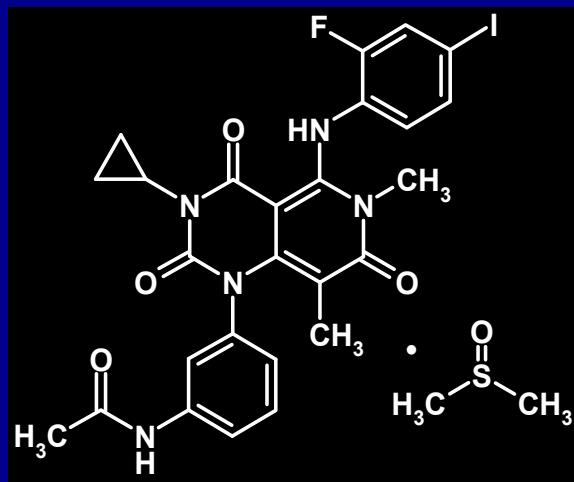
GSK Oncology

***ODAC Pediatric Subcommittee
December 4, 2012***

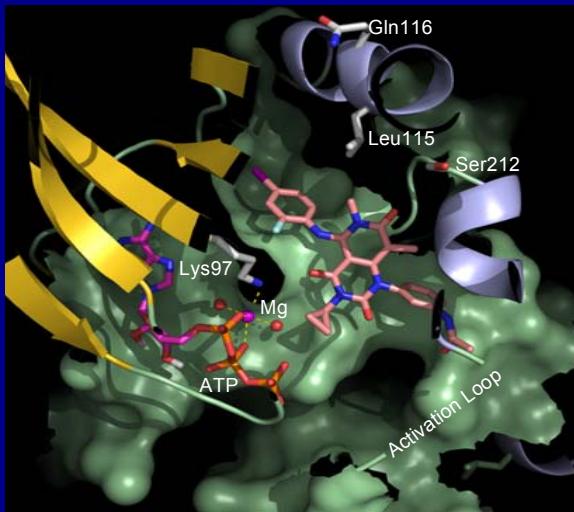
Cellular Signal Transduction: The MAP-Kinase Pathway



Trametinib: Key Characteristics

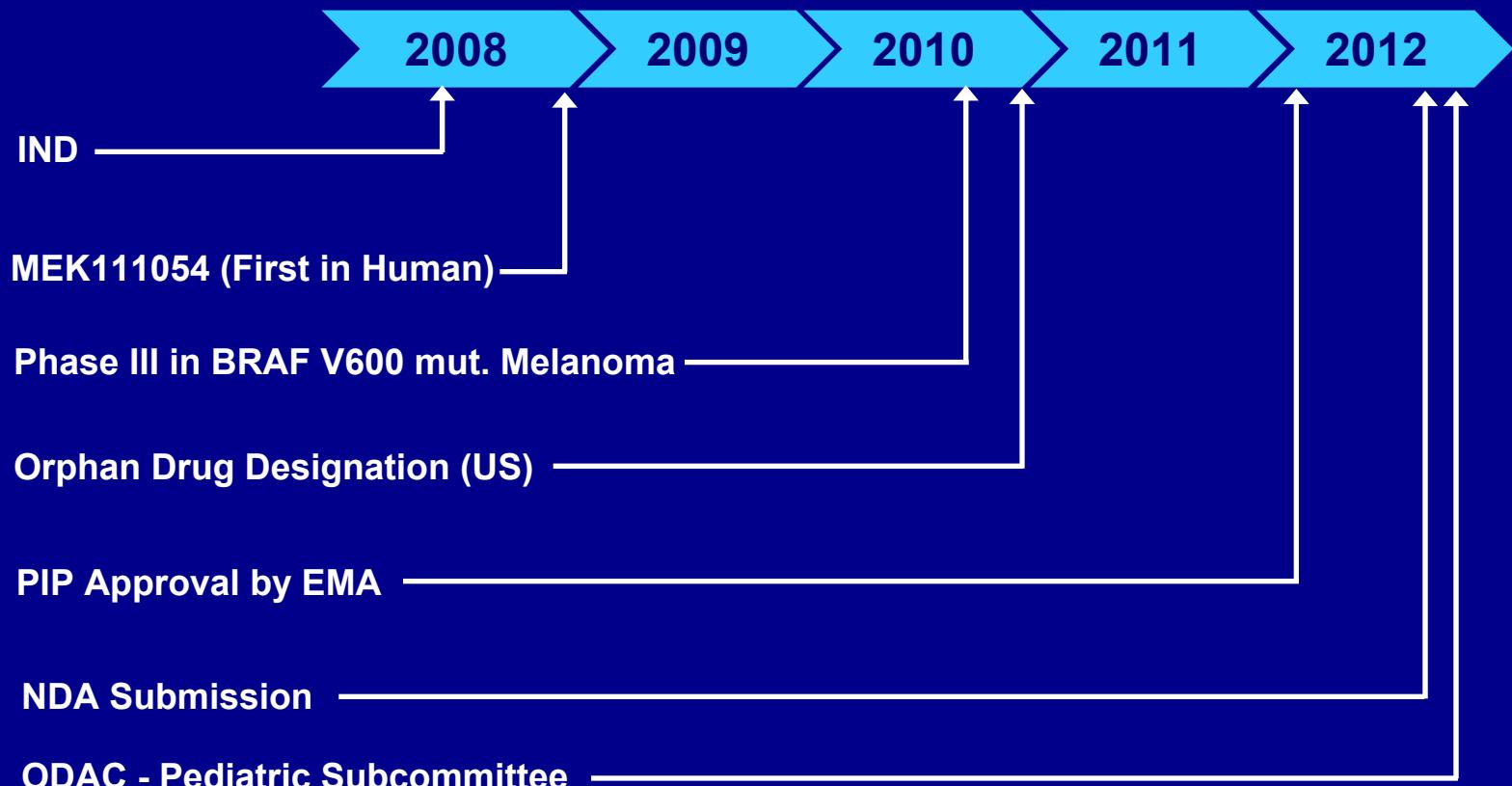


- Pyrido-pyrimidine derivative
- Orally bioavailable as DMSO-solvate
- MW = 693.54 g/mol
- Clinical Phase I – III development



- Inhibition of kinase activation (IC_{50} 0.6 nM) and kinase activity (IC_{50} 10 nM)
- Allosteric inhibitor of serine-threonine kinase MEK-1 and MEK-2
- No off-target activities at concentrations <10 μ M

Trametinib Development: Key Milestones



Trametinib: Dose and Regimen

Recommended: 2 mg administered p.o. once daily (QD)

Exposure & Tolerability:

- MTD is 3 mg QD
- Recommended Phase II/III-dose of 2 mg QD with favorable safety profile

Exposure & Pharmacodynamic Response:

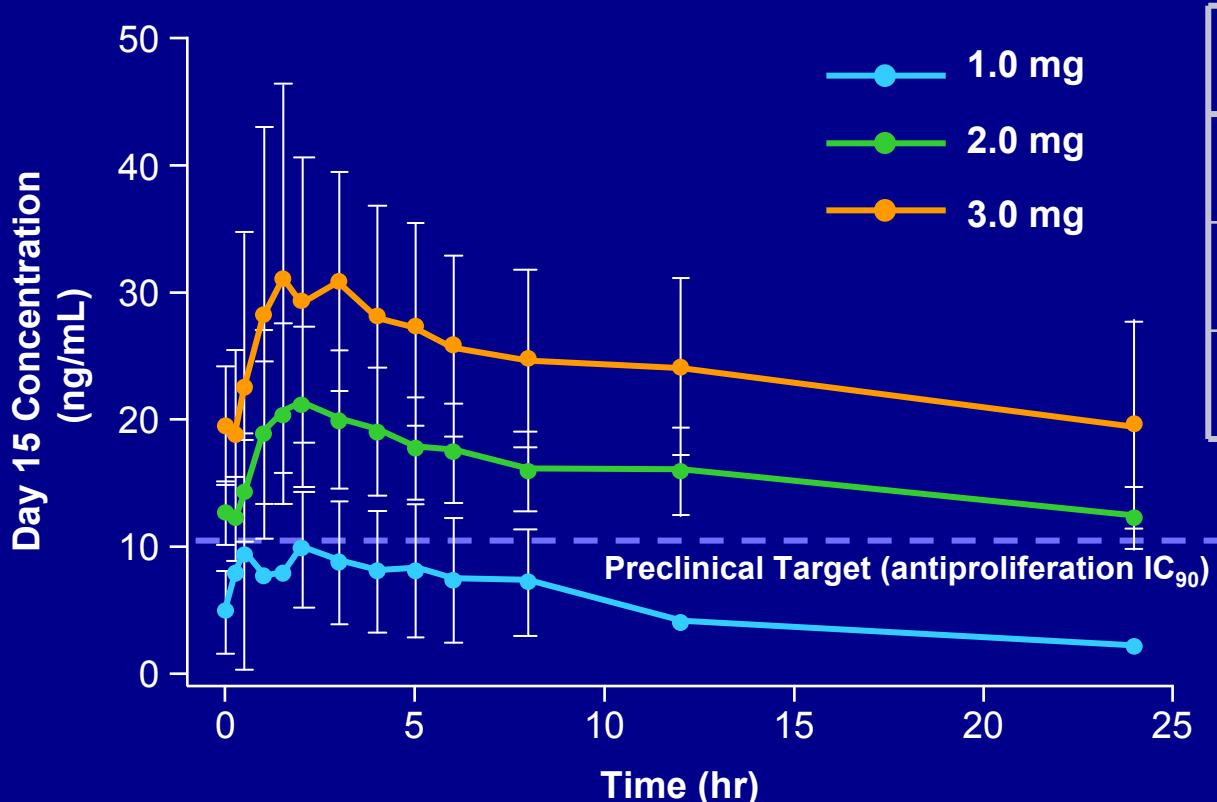
- Dose-dependent FDG-PET response
- Matching Tumor Samples (pre-exposure and steady-state)
 - MAP kinase pathway inhibition (pERK-IHC ↓)
 - Inhibition of cancer cell proliferation (KI67-IHC ↓)
 - Apoptosis Induction (p27^{KIP1} IHC↑)

Exposure & Clinical Response Model Established:

- Tumor size reduction
- Progression-free survival

Trametinib Clinical Pharmacology in Adults

- Long effective half life ($t_{1/2} \sim 5.3$ days)
- Small peak/trough ratio
- Exposure profile is maintained above target C_{trough} over 24 hours
- Low inter-subject variability



2 mg QD (n=14)	Mean	CV%
AUC (ng*hr/mL)	360	31
C _{max} (ng/mL)	23.3	25
C _{trough} (ng/mL)	12.3	19

↓
Foundation for
Exposure-Response
Model

Trametinib Clinical Pharmacology in Adults

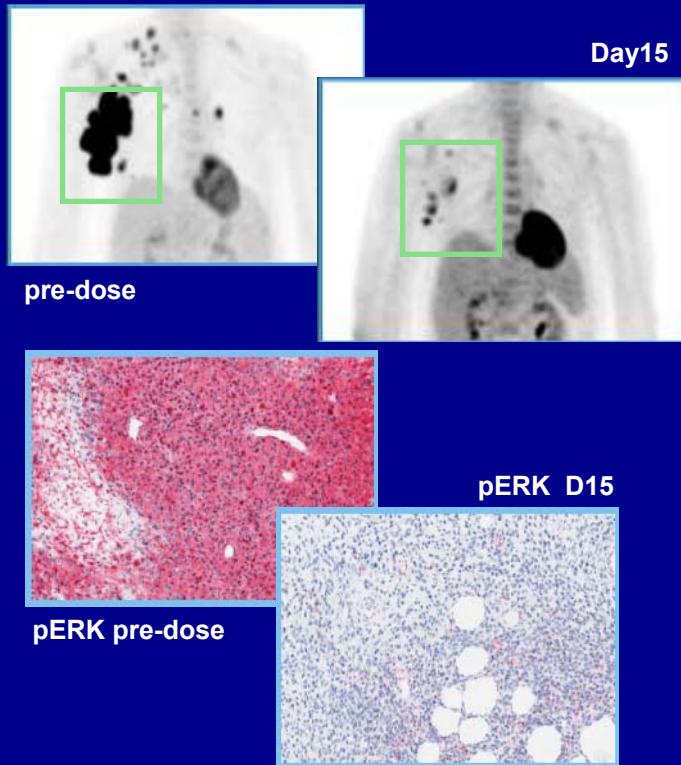
- **Absorption**
 - Tmax = 1.5 hrs
 - Absolute bioavailability moderate to high
 - Bioavailability decreases with a high-fat diet
 - Trametinib is taken fasting, 1 hr before or 2 hrs after a meal
 - Dose Proportional Cmax/AUC(0- τ) after repeat dosing
- **Elimination / Excretion**
 - Steady state by Day 15
 - Fecal excretion as major (~ 80%) route of elimination
- **Metabolism**
 - Liver metabolism through deacetylation (non-CYP450 mediated) with:
 - secondary oxidation or
 - glucuronidation biotransformation pathways
- **Drug-Drug Interactions**
 - Low risk of DDI
 - no CYP interactions
 - not a substrate for P-gp or BCRP

Trametinib Clinical Pharmacology in Adults

- **Renal impairment** – mild and moderate renal impairment – no effect on trametinib exposure
- **Hepatic impairment** – mild hepatic impairment – no effect on trametinib exposure
 - No data available in patients with moderate or severe hepatic impairment
- **Impact of Demographic Factors**
 - Gender and body weight influence trametinib oral clearance (CL/F)
 - Exposure higher in smaller female subjects
 - Exposure lower in heavier male subjects
 - Differences not clinically relevant - dosage adjustment not required
 - Age (≤ 65 vs. >65) has no relevant clinical effect on trametinib PK

Trametinib: Phase I and II Experience in BRAF V600 Mutant Melanoma

Phase I: MEK111054

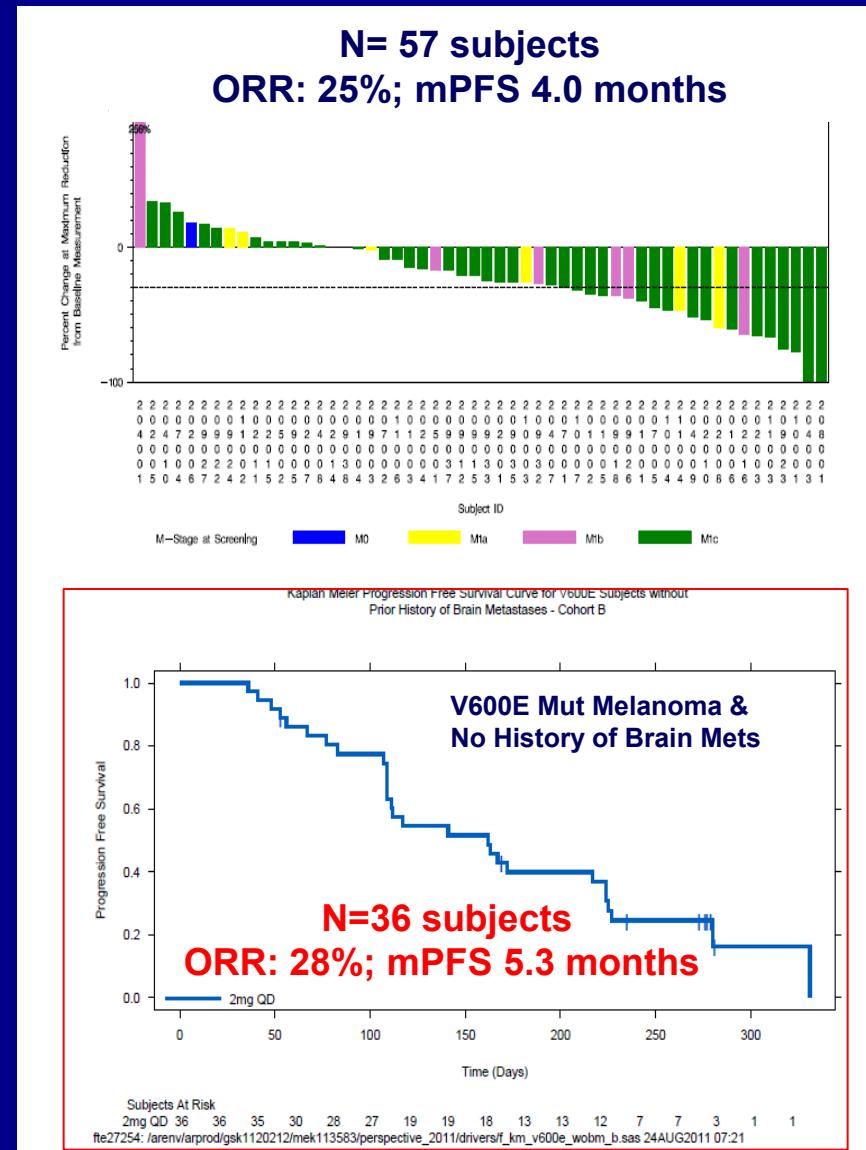


N = 30 subjects

ORR: 40%

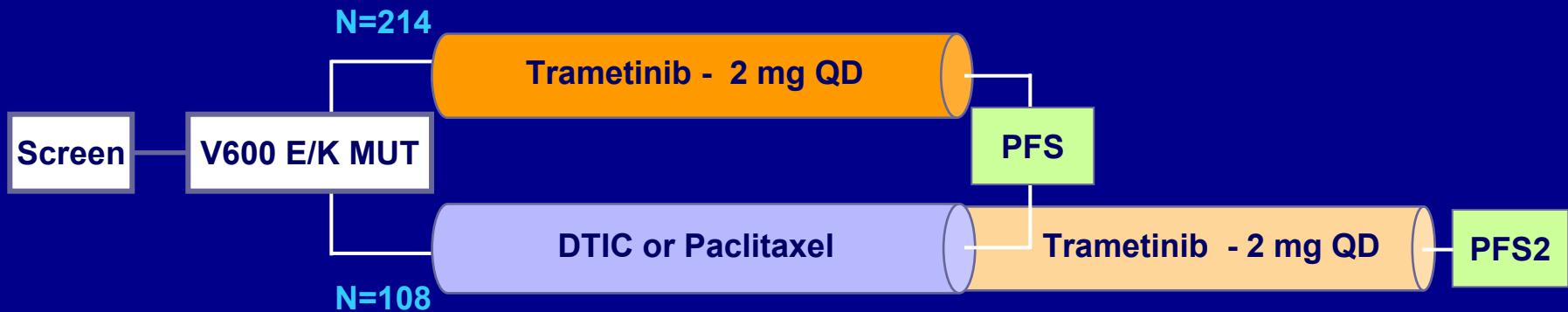
mPFS : 5.7 months

Phase II: MEK113583



Trametinib Phase III Experience

MEK114267 (METRIC) Study Design



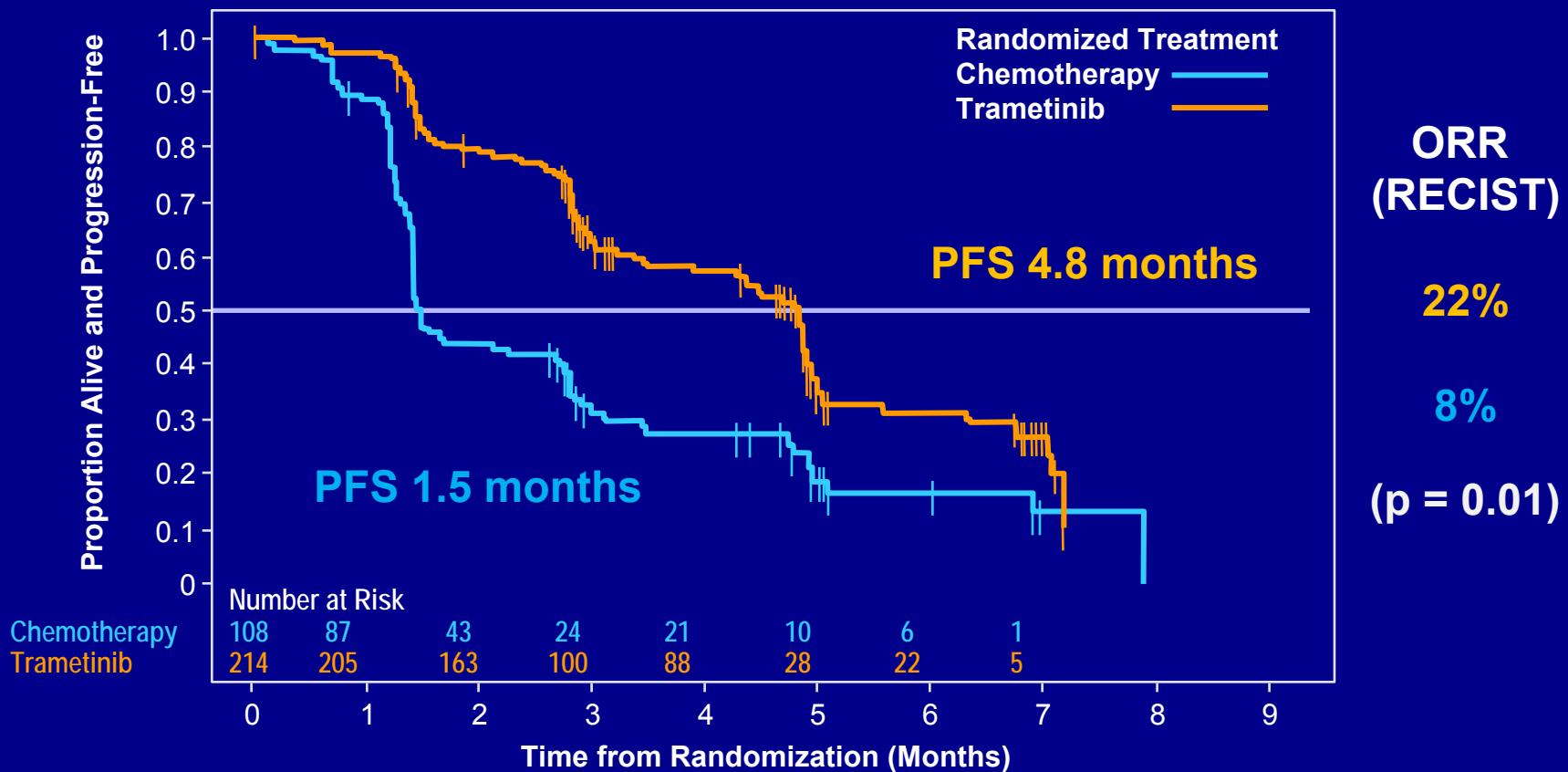
Key study design features: 2:1 randomization;
cross-over after confirmation of disease progression

Population: Prospectively selected for BRAF V600E/K;
≤ 1 prior chemotherapy,

Primary endpoints: PFS in BRAF V600E mutant melanoma without prior history of brain metastases

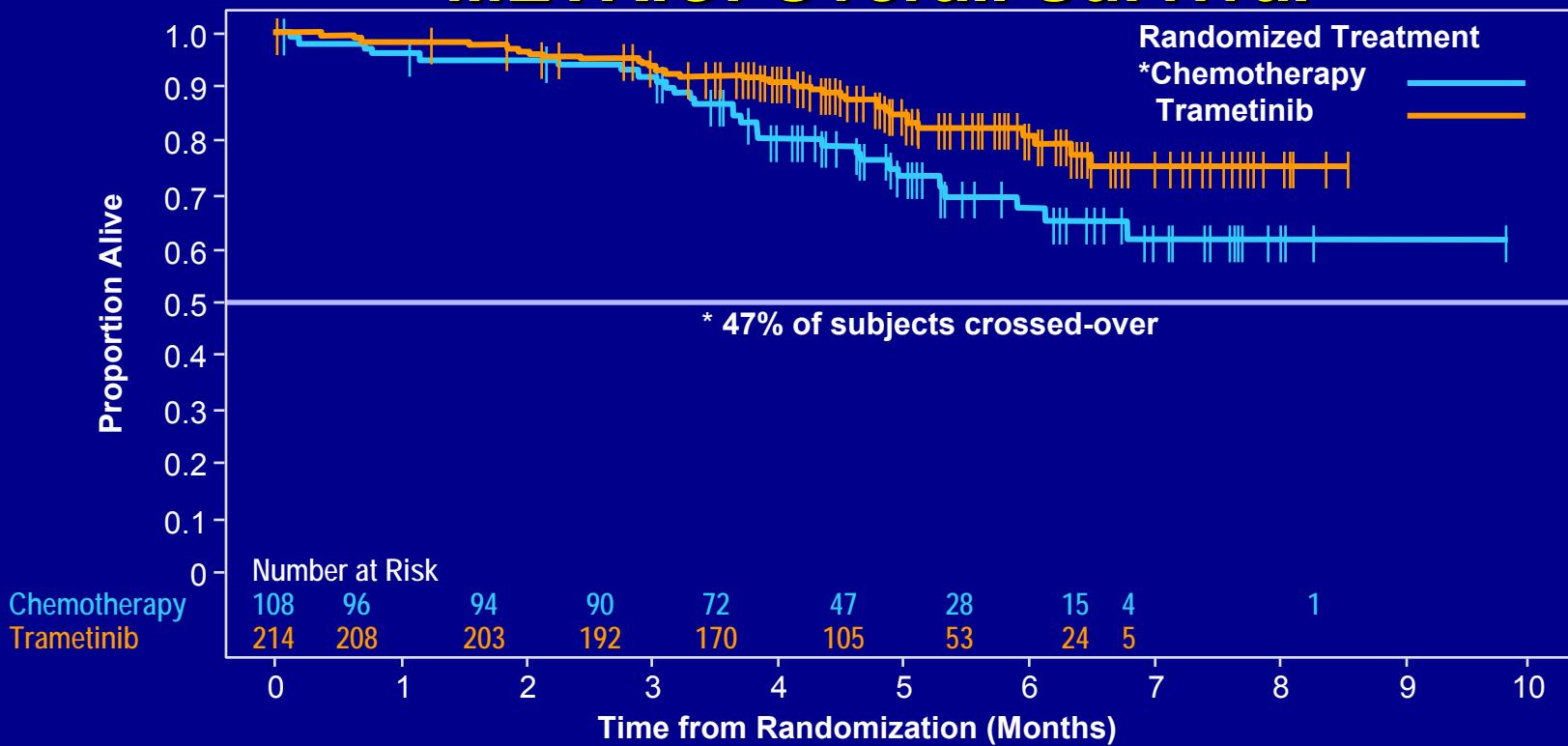
Secondary endpoints: ITT / BRAF V600K population - PFS, OS, ORR, DR
ITT - safety, companion diagnostic, Quality of Life

Trametinib Efficacy in Adults METRIC: Progression-Free Survival



HR (95% CI)	0.45 (0.33, 0.63)
P-value	< 0.0001

Trametinib Efficacy in Adults METRIC: Overall Survival



ITT	Trametinib	Chemotherapy
N	214	108
Died	35 (16%)	29 (27%)
Median (months)	--	--
HR (95% CI) P-value	0.54 (0.32, 0.92) 0.0136	
6 Month Rate (95% CI)	81% (73%, 86%)	67% (55%, 77%)

Safety: Frequent Adverse Events in BRAF V600 Mutant Melanoma

Preferred Term	Integrated Trametinib Studies (N=329)				
	Maximum Grade				
	1	2	3	4	Any Grade
Any event, n (%)	54 (16)	119 (36)	129 (39)	19 (6)	326 (>99)
Rash	102 (31)	62 (19)	22 (7)	1 (<1)	187 (57)
Diarrhea	129 (39)	30 (9)	4 (1)	0	163 (50)
Edema peripheral	76 (23)	20 (6)	5 (2)	0	101 (31)
Dermatitis acneiform	34 (10)	32 (10)	6 (2)	0	72 (22)
Pruritus	43 (13)	3 (<1)	5 (2)	0	51 (16)
Hypertension	4 (1)	14 (4)	27 (8)	0	45 (14)

Grade 5: Study MEK113583=gastrointestinal fistula (1 subject); Study MEK114267=hepatic failure and renal failure (1 subject); myocardial infarction; renal failure; duodenal perforation (1 subject each).

Safety: Adverse Events

Cardiac Adverse Events

- Cardiac Adverse Events (9%)
 - Ejection fraction decrease (5%)
 - Left ventricular dysfunction (3%)
 - Cardiac failure (< 1%)

LVEF decrease \geq 10% from baseline and below LLN: 9%

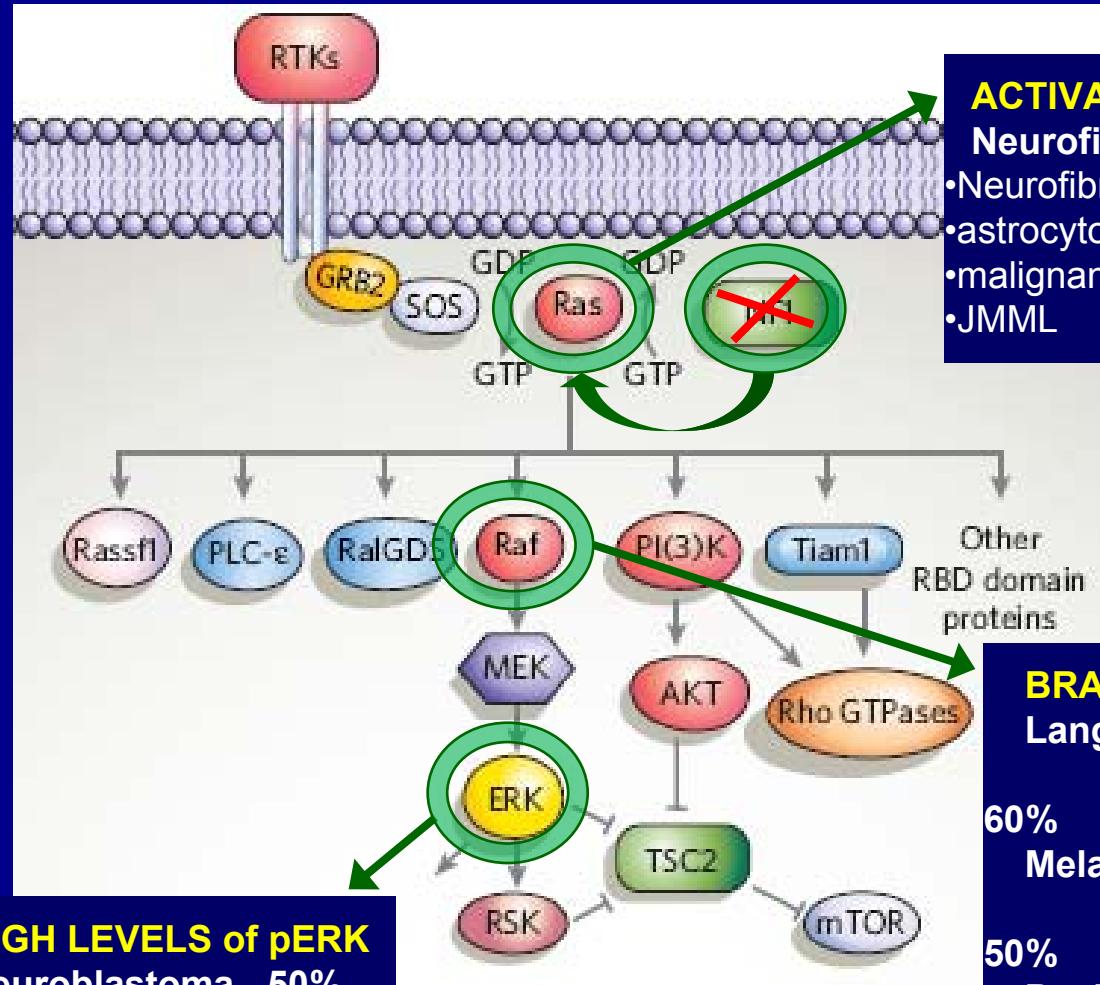
Ocular Adverse Events

- Ocular Events (12%)
 - Vision blurred (6%)
 - Dry eye (3%)
- Rare Ocular Events (in > 1800 subjects)
 - Central Serous Retinopathy (14 cases)
 - Papilledema (5 cases)
 - Retinal Vein Occlusion (4 cases)

Conclusions – Adult Population

- **Trametinib at 2 mg QD provides manageable safety profile**
 - Common AEs: rash, diarrhea, peripheral edema
 - Rare AEs associated with mode-of-action:
Ejection fraction decrease, Central Serous Retinopathy
- **Trametinib demonstrated clinical efficacy**
 - BRAF V600 mutant melanoma sensitive to trametinib
 - Superior PFS, RR and OS benefit compared to chemotherapy

Pediatric Tumors with Activated MAPK Pathway



ACTIVATED RAS SIGNALING

Neurofibromatosis-related malignancies:

- Neurofibromas
- astrocytomas (particularly optic pathway)
- malignant peripheral nerve sheath tumors
- JMM

BRAF ACTIVATING MUTATIONS

Langerhans cell histiocytosis

60%

Melanoma

50%

Papillary thyroid carcinoma

20%

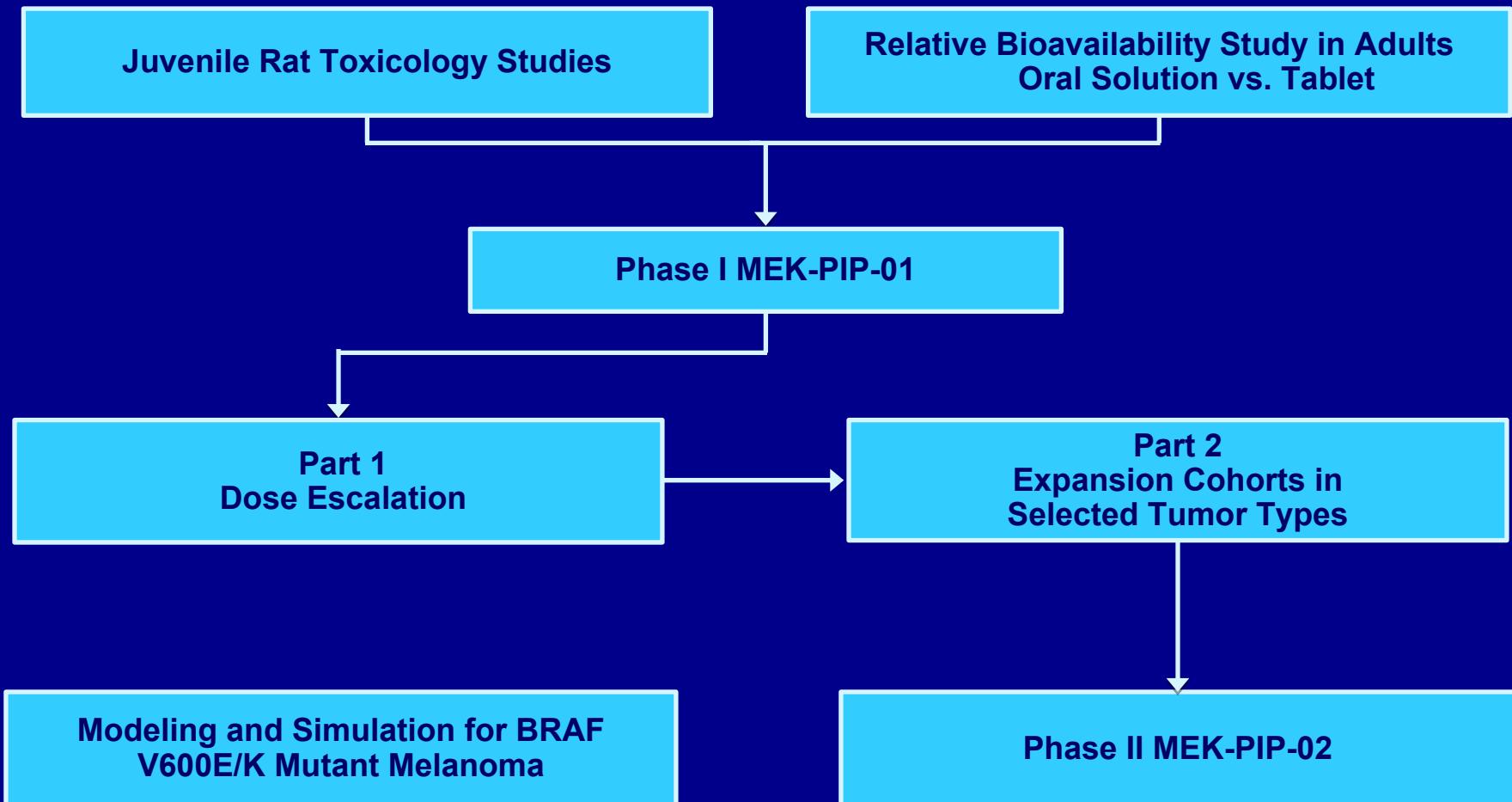
Low- and high-grade gliomas

HIGH LEVELS of pERK
Neuroblastoma - 50%

Pediatric Development: Challenges

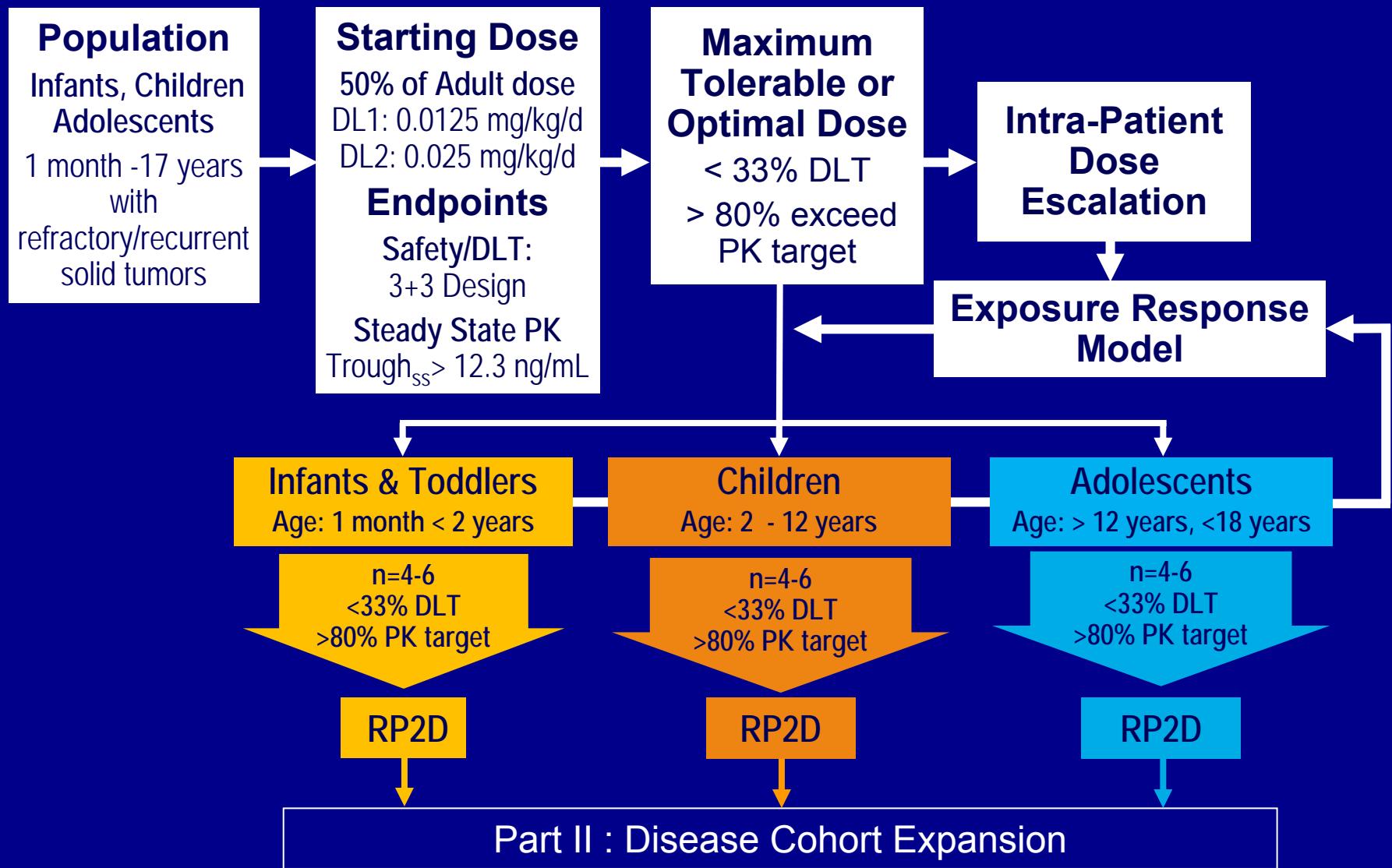
- **Rarity of specific pediatric tumor types**
 - Feasibility
 - Timelines
- **Prospective biomarker assessment**
 - Availability of diagnostic tumor tissue
 - Validated and standardized assay(s)
- **Study Endpoints**
- **Study Design Statistical Power**

Trametinib Pediatric Development Plan



Phase I Study Concept

Part I – Dose Escalation



DL: Dose Level

RP2D: Recommended Phase 2 Dose

DLT: Dose Limiting Toxicity

Phase I Study Concept

Part II – Cohort Expansion

Design

- **4 Disease-specific Expansion Cohorts**
- **10 Patients per cohort**

Objectives

- **Early efficacy (i.e. $\geq 10\%$ tumor response)**
- **Safety and tolerability**
- **Biomarker assessment (i.e. MAP-Kinase pathway activation)**

Phase II Study Concept

- **Randomized study against appropriate comparator if feasible**
- **Tumor type selection based on Phase 1 (Part II) activity**
- **Study size dependent on tumor type and magnitude of therapy effect**
- **Efficacy endpoint(s) appropriate for tumor type**

Summary

- Non-clinical toxicology studies underway to support pediatric development
- Available pediatric formulation
- Exposure driven dose finding in the absence of DLT
- Expansion into tumor types with activation of the target MAP-Kinase pathway
- Modeling and simulation will be used to extrapolate observed adult melanoma data to pediatric patients